

Consciousness & Sleep





Armed Forces College of Medicine

AFCM



Integrate Lecture on Sleep

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INTENDED LEARNING OBJECTIVES (ILO)



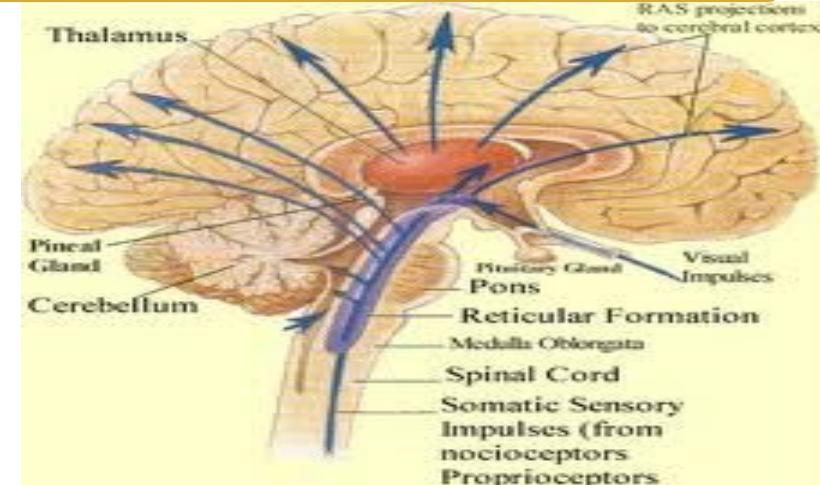
By the end of this lecture the student will
be able to

1. List physiological changes during sleep.
2. Compare & contrast types of sleep.
3. Discuss the mechanisms (theories) of sleep.
4. Explain the sleep/wakefulness cycle .
5. Relate the appropriate hypnotic to its clinical situation
6. Identify important cautions with the use of hypnotics

Consciousness (Wakefulness)



- ✓ It is the awareness of both self & one's surroundings, thoughts and feelings.
- ✓ **Produced** by general excitation of the cerebral cortex as a result of activation of ARAS~~FRF~~ ~~NSTN~~ ~~generalized (+) cerebral cortex~~
(*Reticulo-thalamo-cortical pathway*)
- ✓ **Maintained** by +ve feedback mechanism through re-excitation of ARAS by signals from the activated cerebral cortex.
(*Cortico-thalamo-reticular pathway*)



Sleep

- ✓ It is a physiological state of *temporary* unconsciousness from which person can be aroused by sensory or motor stimuli.



- ✓ Its duration varies inversely with age (average 18 hours in infants, 8 hours in adults and 6 hours in old persons).

PHYSIOLOGICAL CHANGES DURING SLEEP:



- ↓ Heart rate.
- ↓ Vasomotor tone.
- ↓ Blood pressure.



- ↓ rate & depth of breathing.
- ↓ pulmonary ventilation with a ↓ in arterial oxygen levels.
- ↑ ↑ ↑ GIT secretions.
- Most of endocrine secretions ↓ except **Growth hormone ↑** during non-REM sleep.
- ↓ Body temperature.
- ↓ Basal metabolic rate.
- Sensory perception.
- Voluntary movement.
- Reflexes are abolished except a +ve Babinski sign..
- ↓ Muscle tone except ocular.

Mechanisms of sleep

Sleep result from depression of cerebral cortex 2ry to inhibition of ARAS which can occur by either:

1- Passive theory of sleep:

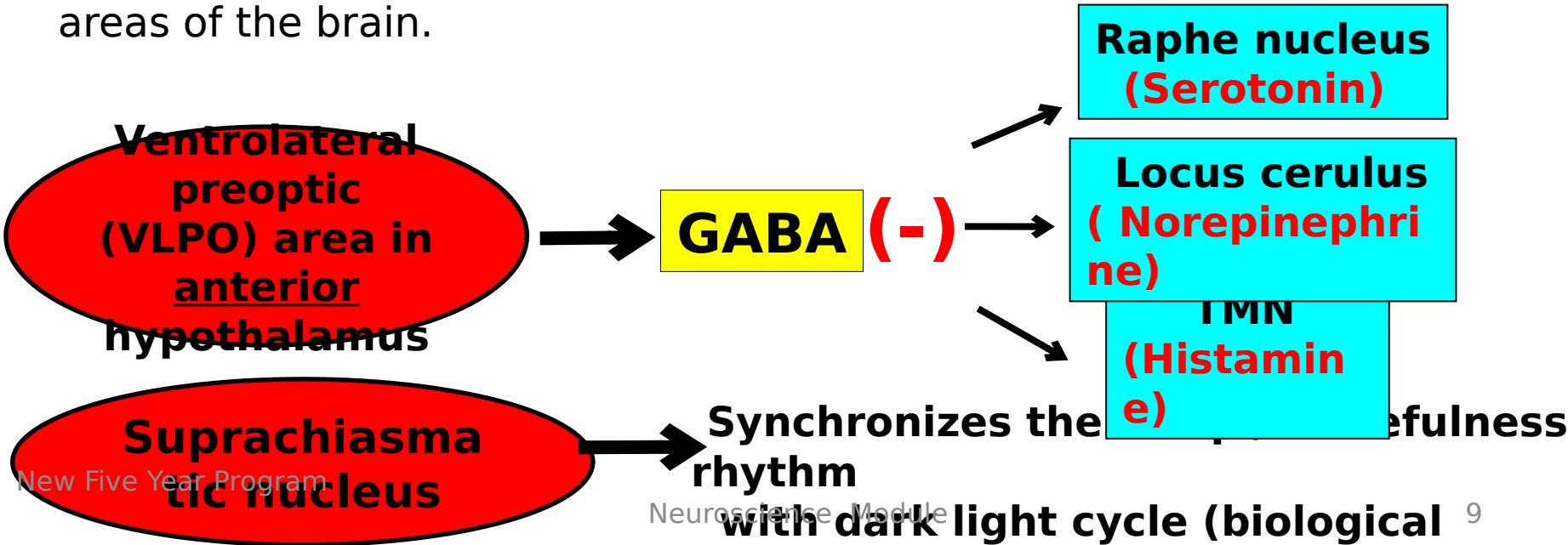
Sleep is caused by passive (-) of ARAS.

- by fatigue after a period of wakefulness
- by elimination of exciting stimuli.

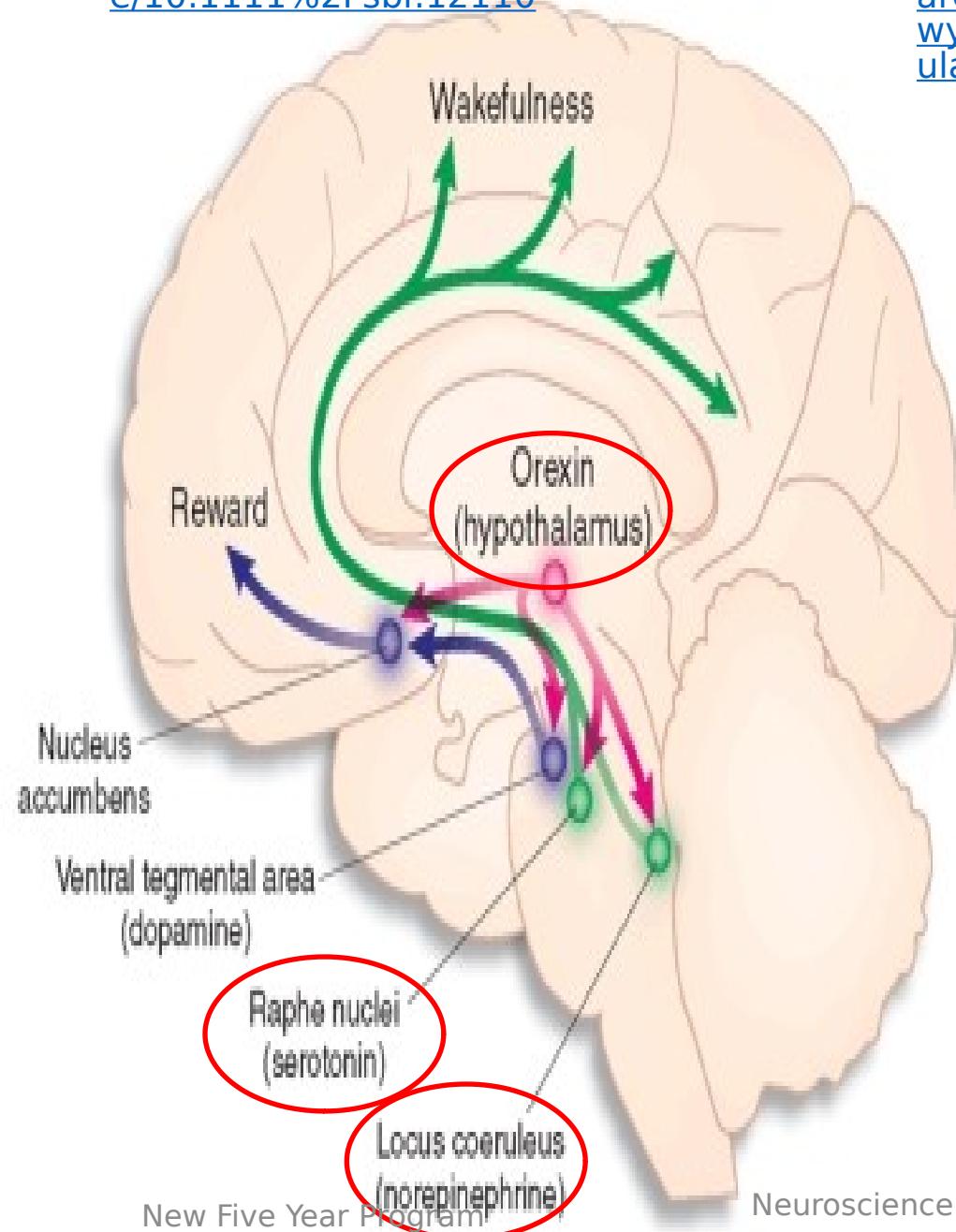


2-Active theory of sleep:

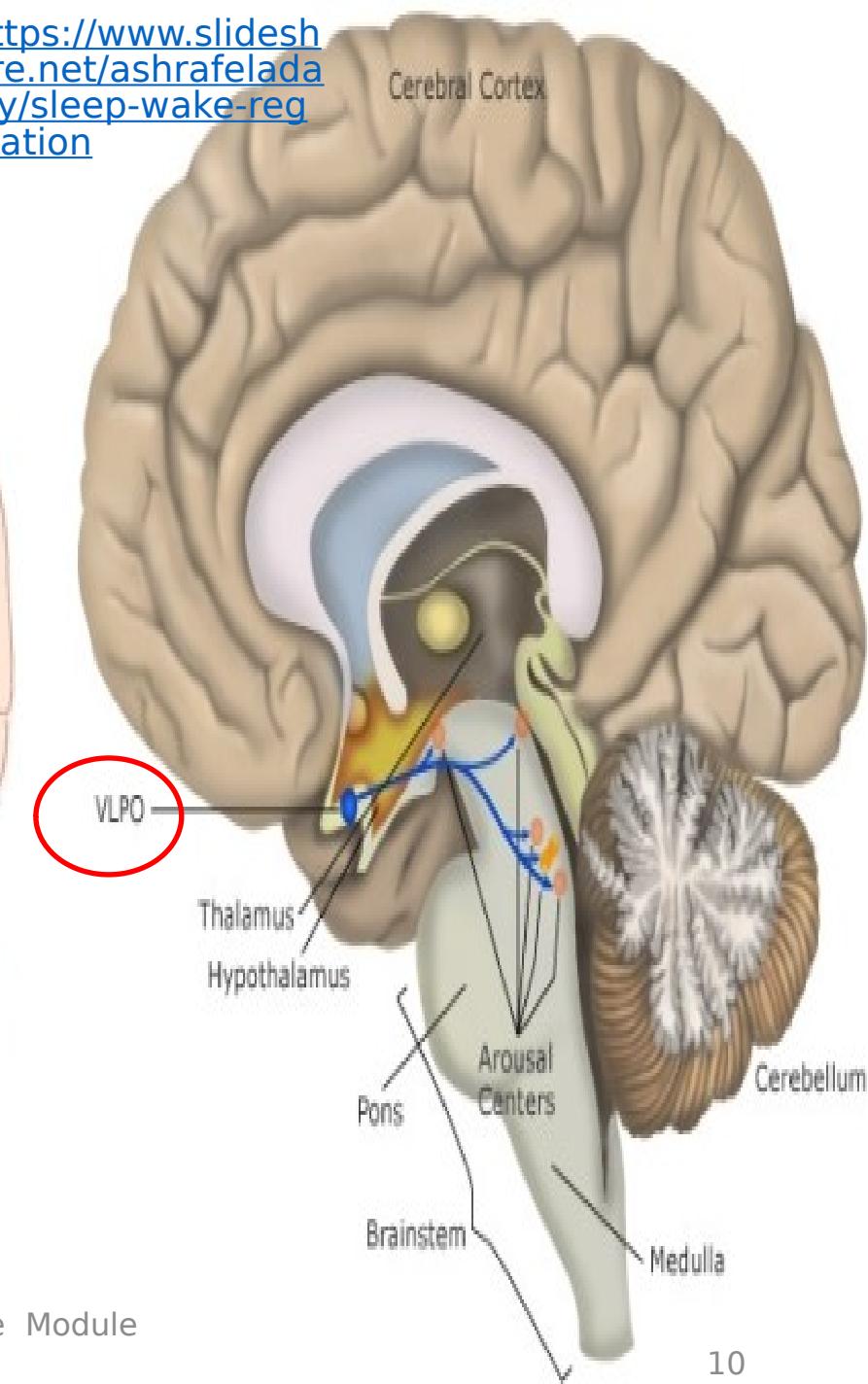
- Many areas with their neurotransmitters are involved in (+) of RAS producing wakefulness as
 - Noradrenaline from locus cerulus.
 - Serotonin from raphe nucleus.
 - Orexins from hypothalamus (LHA).
 - Histamine from post. Hypothalamus (TMN).
- **Orexins** producing neurons projects from the lateral hypothalamus. They strongly excite arousal centers e.g the norepinephrine and histamine systems as well as the cerebral cortex itself with important role in wakefulness.
- Sleep is caused by active inhibition of ARAS by stimulation of specific areas of the brain.



<https://link.springer.com/article/10.1111%2Fsbr.12110>



<https://www.slideshare.net/ashrafeladawy/sleep-wake-regulation>



CATEGORY	NUCLEUS	NEURO-TRANSMITTER	LEVEL OF ACTIVITY	
			during arousal	during sleep
sleep-promoting	VLPO	GABA	0	++
arousal-promoting	LC	norepinephrine	++	0
arousal-promoting	Raphe	serotonin	++	0
arousal-promoting	TMN	histamine	++	0
orexin-releasing	LHA	orexin	++	0



GABA

z z z z

Orexin



NE, Serotonin,
Histamine



Sleep/wakefulness cycle

- Once wakefulness is initiated , it is maintained by +ve feedback excitation of ARAS.
- After wakefulness continue for several hours, sleep occurs due to:
 - 1- Fading away of the +ve FB cycle d.t fatigue of RAS.
 - 2- Activation of sleep centers which (-) RAS.
- During the sleeping hours:
 - 1- ARAS gradually recovers its excitability.
 - 2- Sleep centers become less active.
- So, ARAS is released from their (-) effect & discharge to the cerebral cortex → new cycle of wakefulness.

Melatonin and sleep- wake state



- Melatonin released from pineal gland plays a role in sleep mechanisms.
- Melatonin synthesis and secretion are ↑ during the **dark** hours and maintained at a ↓ level during **daylight** hours.
- The diurnal change in melatonin secretion may function to coordinate events with the light-dark cycle in the environment.

- Retinohypothalamic fibers synapse in the suprachiasmatic nuclei (SCN)

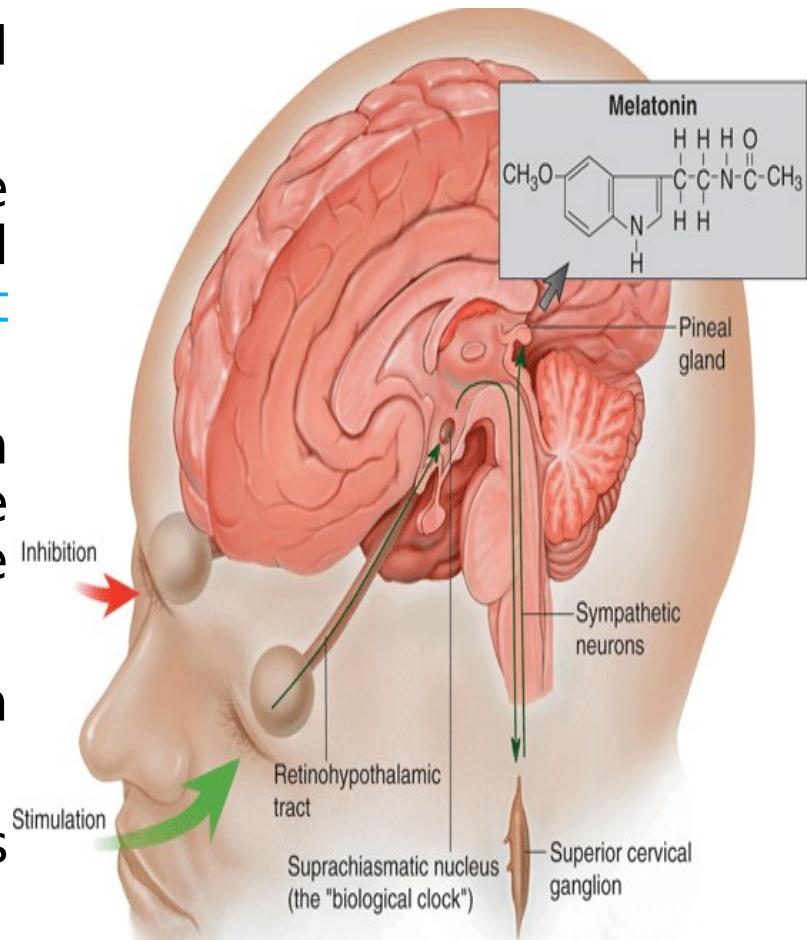
- sympathetic preganglionic neurons in the spinal cord

- superior cervical ganglion.

- Postganglionic neurons project

- the pineal gland

- melatonin secretion

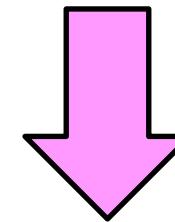
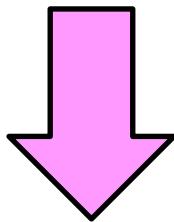


Source: Barrett KE, Barman SM, Boitano S, Brooks H: Ganong's Review of Medical Physiology, 23rd Edition: <http://www.accessmedicine.com>



Types of Sleep

- There are 2 types of sleep that alternate in a cyclic manner during sleep.



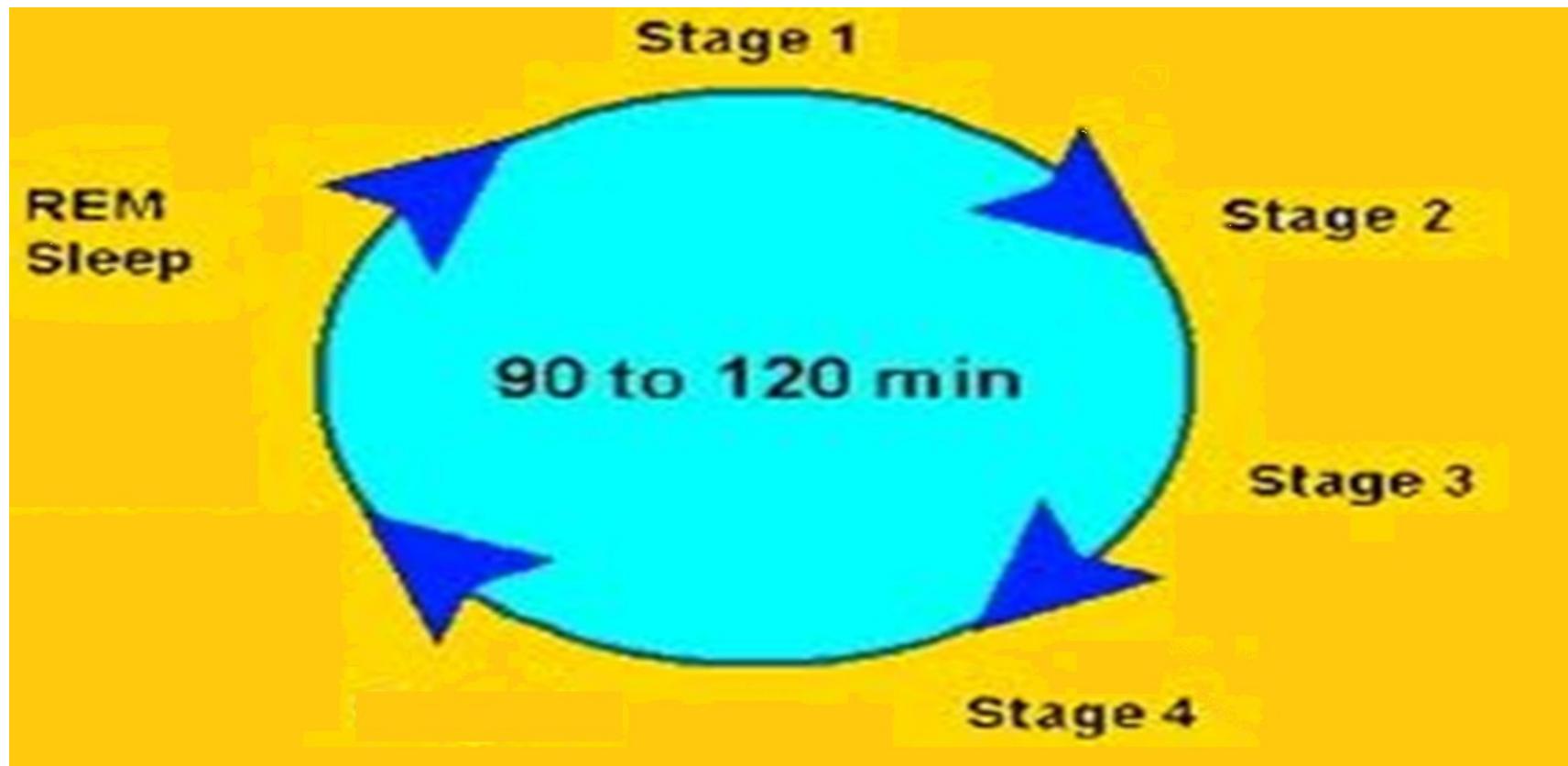
Slow wave sleep
non- rapid eye movement
sleep
= non-REM

Rapid eye movement
sleep
= REM



Types of Sleep

Sleep occurs in cycles of NREM-REM sleep, each lasting approximately 90-110 minutes.





Types of Sleep

**Slow wave sleep
(SWS)**
= non-REM

**Rapid eye
movement sleep**
= REM

Timing

At the start of sleep
~90 minutes
(80% of the total
sleeping time)

After 4th stage of

non REM
~20 minutes
(20% of the total
sleeping time)

**Eye
moveme
nts**

**Eye deviates up
+ miosis**

**Rapid eye
movement**

**Importan
ce**
**Autonom
ic
changes**

Physical rest

↓ HR, ABP, RR & BMR
(relative ↑
parasympathetic
activity).

Mental rest

↑ HR, ABP,.....
(↑ sympathetic
activity).



Types of Sleep

**Slow wave sleep
(SWS)**
= **non-REM**

**Growth
hormon**

**Sleep
talking,
walking &
nocturnal
enuresis**

Dreams

**Teeth
grinding**

**Muscle
tone**

**Rapid eye
movement sleep**
= **REM**



Present

Absent

**Present but not
remembered**

**Active remembered
dreams**

Absent

Present



Marked ↓↓↓
**(Paradoxical
Sleep)**



Types of Sleep

Slow wave sleep (SWS)

= non-REM

Rapid eye movement sleep

= REM

Threshold of arousal

EEG changes

Low
Four stages:

Stage 1: very light sleep (theta waves)

Stage 2: light sleep (sleep spindles within theta)

Stage 3: moderately deep sleep (delta waves)

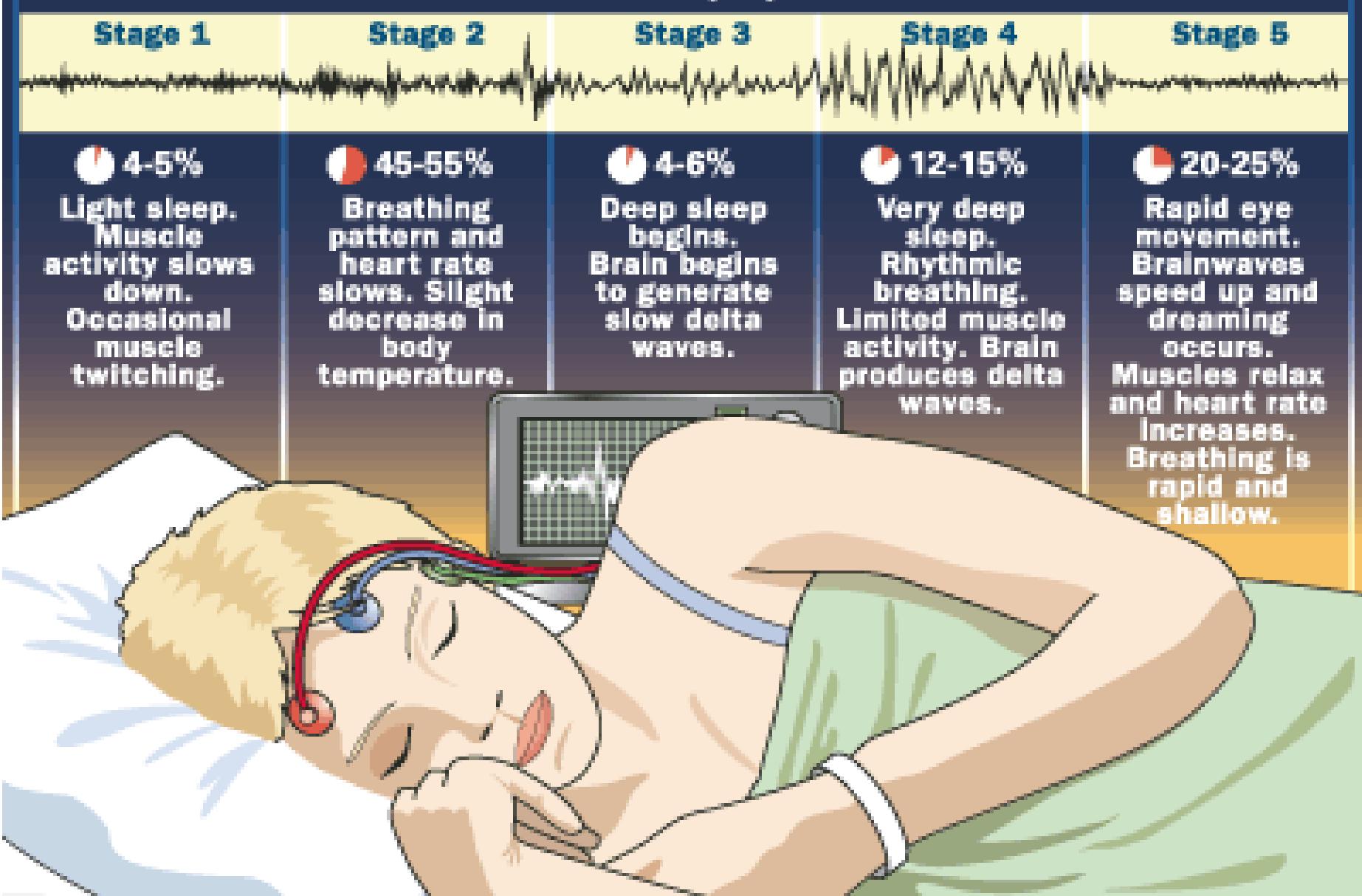
Stage 4: Sleep is deepest (delta waves with maximal slowing)

High

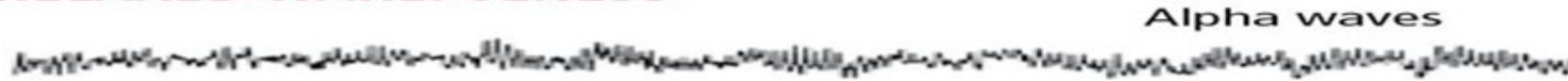
B waves like that in alert state (desynchronized beta rhythm).

Also called **paradoxical sleep** because it indicates marked brain activity but person is still asleep.

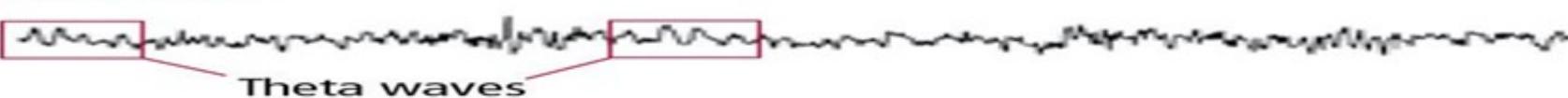
100% Sleep Cycle



RELAXED WAKEFULNESS



STAGE N1



STAGE N2



STAGE N3 or DEEP SLEEP



REM or DREAMING SLEEP



Brain waves change dramatically during the different stages of sleep.

<https://www.helpguide.org/harvard/biology-of-sleep-circadian-rhythms-sleep-stages.htm>

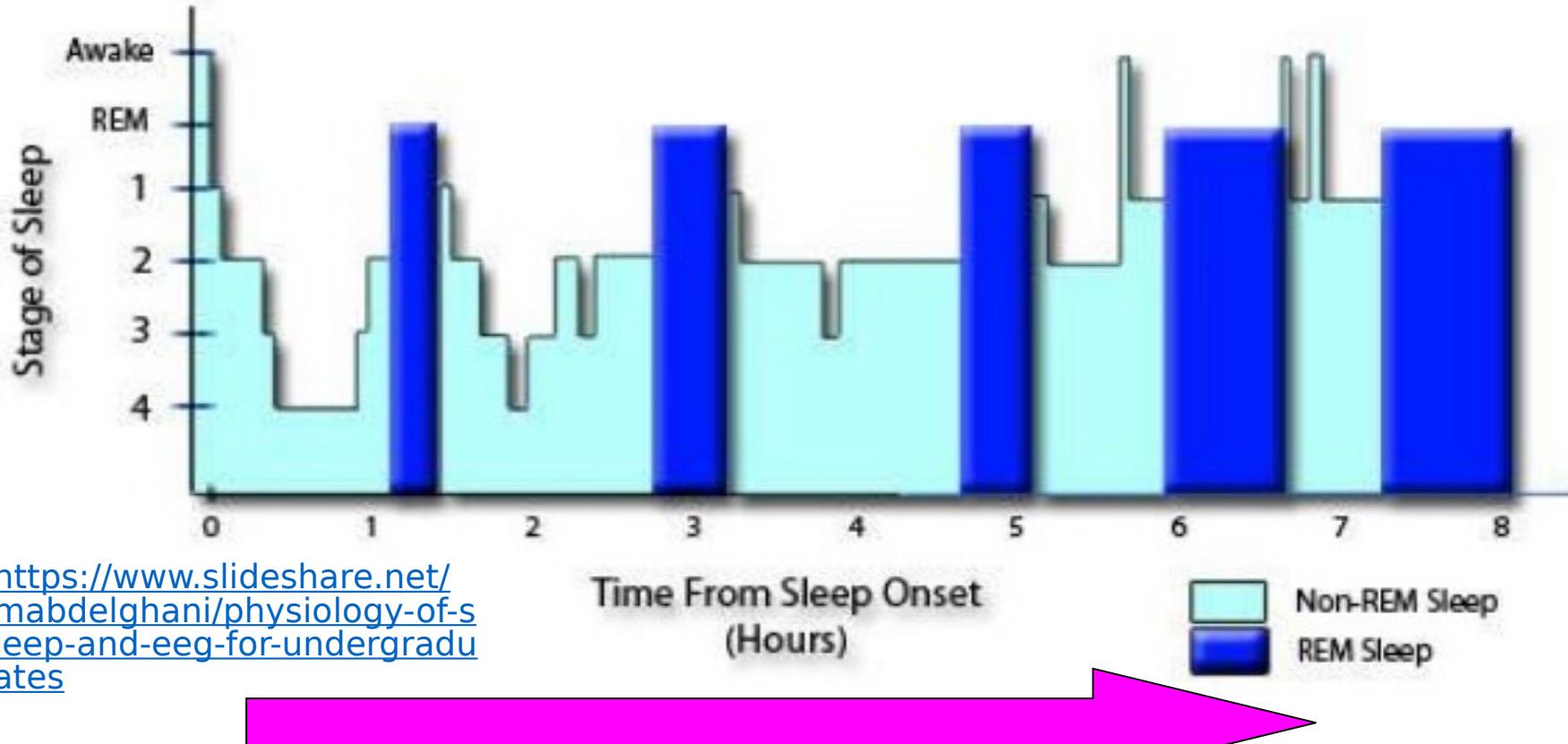
Distribution of sleep stages



- Sleep starts normally by the slow wave type for about 90 minutes, then REM sleep follows for about 20 minutes.
- This is repeated cyclically *with gradual prolongation of the REM sleep periods and less stage 3 and 4 sleep* towards morning.
- Therefore, there are 4-6 sleep cycles *during a single night and the REM sleep constitutes 20 % of total sleep time.*

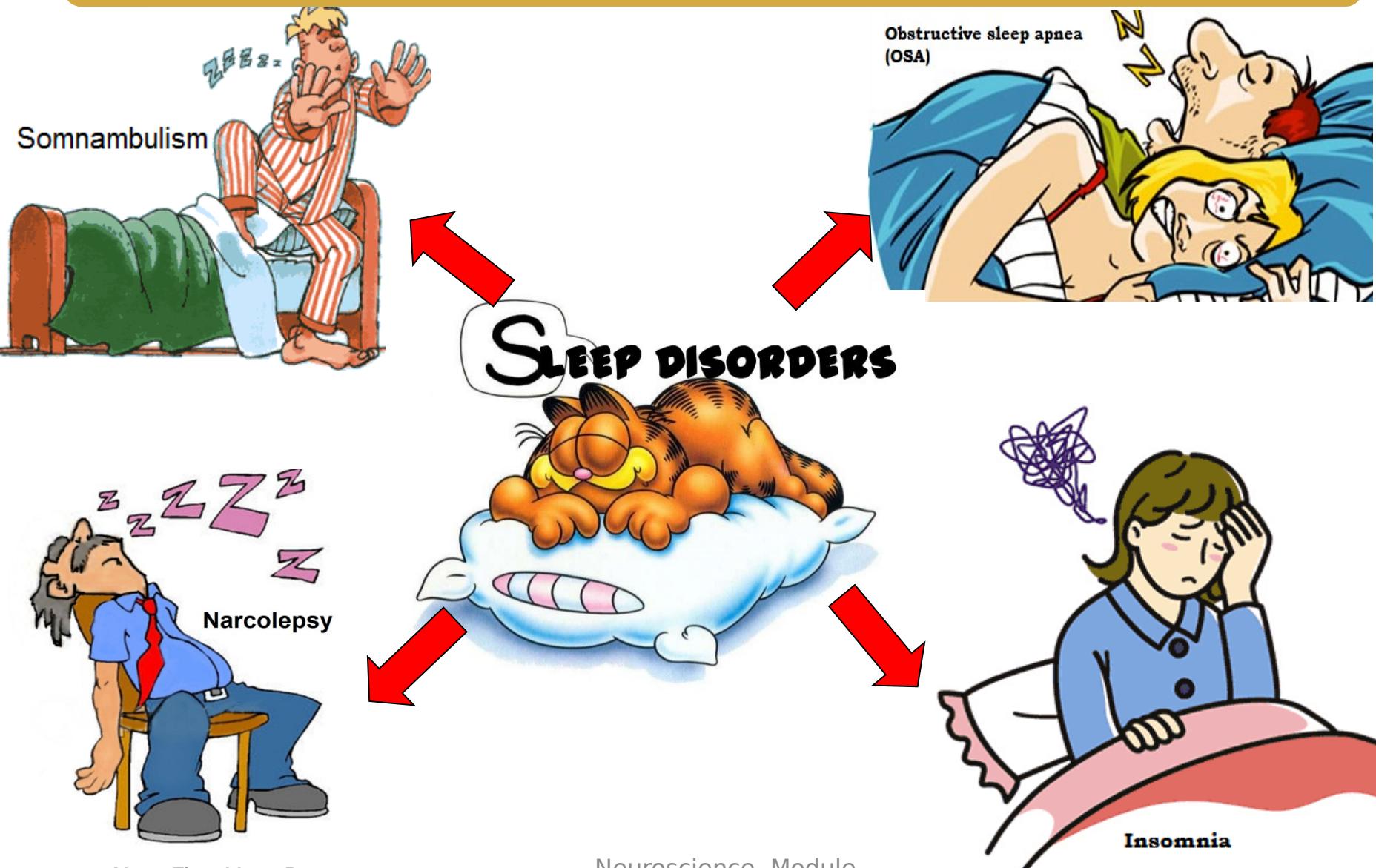
DISTRIBUTION OF SLEEP STAGES

Sleep Stages Through The Night



↑ REM
↓ SWS (stage 3&4)

Sleep Disorders



Sleep Disorders



- Narcolepsy: an eventual irresistible urge to sleep during daytime. It may be related to decrease in orexin in the hypothalamus.
- Obstructive sleep apnea: is the most common cause of daytime sleepiness due to fragmented sleep at night.

Episodes of obstruction of the upper airway (due to reduction in muscle tone) □ cessation of breathing □ brief arousals from sleep in order to reestablish upper airway tone.

- Somnambulism: Sleep walking.
- Nocturnal enuresis: bed wetting during sleep.
- Insomnia: lack of sleep.

Sleep Hygiene



- Establish a set bedtime routine.
- Set a regular sleep and wake time.
- Go to bed when tired & get out of bed if unable to sleep **within 15 minutes.**
- Reduce noise, light, stimulation, & temperature in bedroom.
- Restrict activities in bed to those that help induce sleep.

Sleep Hygiene



- Limit use of alcohol or tobacco.
- Do not exercise or participate in vigorous activities in the evening.
- Exercise during the day.
- Eat a balanced diet.
- Increase exposure to natural and bright light during the day.
- Educate self about normal sleep and sleep behavior

Treatment of sleep disorders



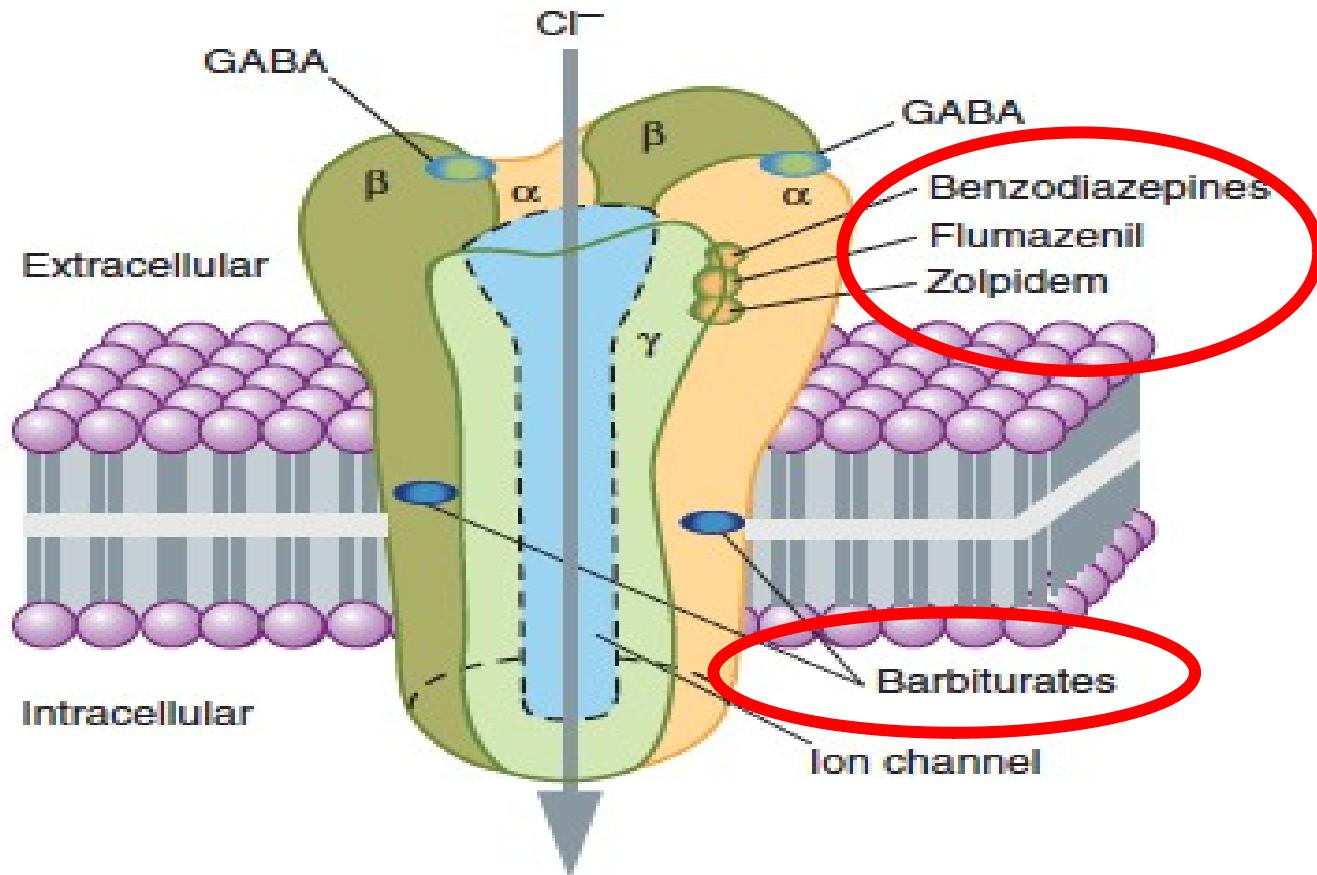
1. Treatment of underlying medical conditions or psychiatric illness
2. Non-pharmacologic therapies are very important.
3. Some patients will still need and should be given a sedative-hypnotic **for a limited period**.
4. Abrupt discontinuance of many drugs in this class can lead to rebound insomnia
5. The failure of insomnia to remit after 7–10 days of treatment may indicate the presence of a primary psychiatric or medical illness that should be evaluated.

6. Long-term use of hypnotics is an irrational and dangerous medical practice.

Molecular Pharmacology of hypnotics



Reminder





Benzodiazepines

(Some are used as hypnotics)

Triazolam

Lorazepam

Temazepam

Alprazolam [XANAX]

Bromazepam [CALMEPAM]

Antihistamines

- Diphenhydramine
- Hydroxyzine
- Promethazine

Hypnotics

Zolpidem Zaleplon Eszopiclone

Barbiturates

“Their use for insomnia is no longer accepted, given their adverse effects and potential for tolerance”

Bind more selectively because these drugs interact only with GABA_A-receptor isoforms that contain α_1 subunits

Rapid onset of action and hypnotic effect for approximately 5 hours

Tolerance less than that of zaleplon t_{1/2} of six hours

Fewer effects on cognitive function compared to zolpidem or the benzodiazepines
Minimal tolerance, Half life of one hour

Ramelteon

A selective agonist at the MT₁ and MT₂ receptors.

For increased sleep latency, Minimal potential for abuse

Suvorexant

An orexin antagonist that improves sleep duration

PHENADONE: Chlorpheneramine Maleate 40mg / 100ml, Dexamethasone 10mg / 100ml

Combined Antihistaminic with Systemic Corticosteroid

Treatment of sleep disorders-Drug choice



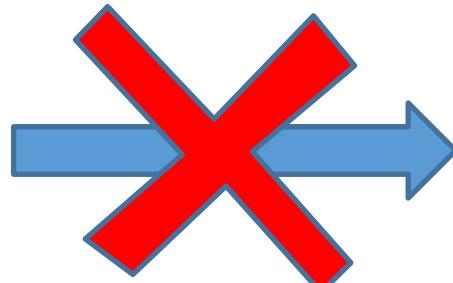
1. Benzodiazepines can cause a dose-dependent decrease in both REM and slow-wave sleep but less than that produced by barbiturates.
2. The newer hypnotics, zolpidem, zaleplon, and eszopiclone, are less likely than the benzodiazepines to change sleep patterns.

OTHER HYPNOTIC AGENTS- BZ₁ agonists

Reminder



- At usual hypnotic doses, the non-benzodiazepine drugs:
 - Zolpidem
 - Zaleplon
 - Eszopiclone



- Do not significantly alter the various sleep stages and, hence, are often the preferred hypnotics.

This may be due to their relative selectivity for the BZ1 receptor.

All three agents are controlled substances.

Treatment of sleep disorders- Drug choice



For patients with sleep onset insomnia

A relatively short-acting medication
(duration of effect \leq 8 hours)

- Zaleplon
- Zolpidem
- Triazolam
- Ramelteon

For patients with sleep maintenance insomnia

A longer-acting medication is preferable

- Zolpidem (extended release)
- Eszopiclone
- Lorazepam
- Suvorexant

For patients with awakening in the middle of the night

- Zaleplon
- A specific sublingual tablet form of zolpidem

(at least four hours of time in bed remaining after administration)

Treatment of sleep disorders- Cautions



1. A dose that **does not impair** mentation or motor functions during waking hours.
2. Prescriptions should be written for **short periods**
3. Assess the **efficacy of therapy** from the patient's subjective responses.
4. **Combinations** of antianxiety agents should be **avoided**
5. Patients should be cautioned about the **consumption of alcohol** and the concurrent use of **over-the-counter medications** containing antihistaminic or anticholinergic drugs
6. Excessive CNS effects in **the elderly**: "*The most common reversible cause of confusional states in the elderly is overuse of sedative/hypnotics.*"
7. Increased **sensitivity to sedative-hypnotics** is more common in patients with cardiovascular disease, respiratory disease, or hepatic impairment

Controlled use of sedatives and hypnotics and notes about addiction



1. Most sedative-hypnotic drugs are classified as Schedule III or Schedule IV drugs
2. Consequences of abuse are both psychological and physiologic.
3. “Physiologic dependence can be described as an altered physiologic state that requires continuous drug administration to prevent an abstinence or withdrawal syndrome”
4. Withdrawal symptoms depend on the magnitude of the dose used immediately before cessation of use.
5. Less symptoms with longer acting agents

SUGGESTED TEXTBOOKS



- ❖ Ganong's Review of Medical Physiology , 23rd edition, Chapter 15.
- ❖ Guyton & Hall: Textbook of Medical Physiology, 12e [pages: 1349-1353]
- ❖ Sleep Disorders (Oxford Psychiatry Library)
(2 ed.) Chapter 6

SUGGESTED FURTHER READING



1. Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.
2. Jet lag. In: UpToDate
 - . https://www.uptodate.com/contents/jet-lag?search=jey%20lag§ionRank=3&usage_type=default&anchor=H3721224068&source=machineLearning&selectedTitle=1~150&display_rank=1#H1915420610
. Accessed on 27 Nov, 2019.
3. Management of Obstructive Sleep Apnea. In: UpToDate.
https://www.uptodate.com/contents/management-of-obstructive-sleep-apnea-in-adults?search=obstructive%20sleep%20apnea&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2#H16
. Accessed on 27 Nov, 2019.

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thank you!

